



1
SEQUENCE LISTING

RECEIVED

OCT 24 2001

TECH CENTER 1600/2900

<110> YUI, MASAKI
YOKOZAWA, AKIRA
MURATA, TOMOYO
TSURUTA, KAZUHISA
SHIMIZU, HIROTOMO

<120> METHOD FOR KEEPING THE QUALITY OF AQUEOUS PARENTERAL
SOLUTION OF THROMBOMODULIN IN STORAGE AND DISTRIBUTION

<130> KP-8753

<140> 09/509,994

<141> 2000-05-08

<150> PCT/JP98/04609

<151> 1998-10-13

<150> JP 9-281659

<151> 1997-10-15

<150> JP 9-308523

<151> 1997-11-11

<160> 6

<170> PatentIn Ver. 2.1

<210> 1

<211> 516

<212> PRT

<213> Homo sapiens

<220>

<223> Partial amino acid sequences of a human
thrombomodulin

<400> 1

Met Leu Gly Val Leu Val Leu Gly Ala Leu Ala Leu Ala Gly Leu Gly
1 5 10 15

Phe Pro Ala Pro Ala Glu Pro Gln Pro Gly Gly Ser Gln Cys Val Glu
20 25 30

His Asp Cys Phe Ala Leu Tyr Pro Gly Pro Ala Thr Phe Leu Asn Ala
35 40 45

Ser Gln Ile Cys Asp Gly Leu Arg Gly His Leu Met Thr Val Arg Ser
50 55 60

Ser Val Ala Ala Asp Val Ile Ser Leu Leu Leu Asn Gly Asp Gly Gly
65 70 75 80

Val Gly Arg Arg Arg Leu Trp Ile Gly Leu Gln Leu Pro Pro Gly Cys
85 90 95

Gly Asp Pro Lys Arg Leu Gly Pro Leu Arg Gly Phe Gln Trp Val Thr
 100 105 110
 Gly Asp Asn Asn Thr Ser Tyr Ser Arg Trp Ala Arg Leu Asp Leu Asn
 115 120 125
 Gly Ala Pro Leu Cys Gly Pro Leu Cys Val Ala Val Ser Ala Ala Glu
 130 135 140
 Ala Thr Val Pro Ser Glu Pro Ile Trp Glu Glu Gln Gln Cys Glu Val
 145 150 155 160
 Lys Ala Asp Gly Phe Leu Cys Glu Phe His Phe Pro Ala Thr Cys Arg
 165 170 175
 Pro Leu Ala Val Glu Pro Gly Ala Ala Ala Ala Val Ser Ile Thr
 180 185 190
 Tyr Gly Thr Pro Phe Ala Ala Arg Gly Ala Asp Phe Gln Ala Leu Pro
 195 200 205
 Val Gly Ser Ser Ala Ala Val Ala Pro Leu Gly Leu Gln Leu Met Cys
 210 215 220
 Thr Ala Pro Pro Gly Ala Val Gln Gly His Trp Ala Arg Glu Ala Pro
 225 230 235 240
 Gly Ala Trp Asp Cys Ser Val Glu Asn Gly Gly Cys Glu His Ala Cys
 245 250 255
 Asn Ala Ile Pro Gly Ala Pro Arg Cys Gln Cys Pro Ala Gly Ala Ala
 260 265 270
 Leu Gln Ala Asp Gly Arg Ser Cys Thr Ala Ser Ala Thr Gln Ser Cys
 275 280 285
 Asn Asp Leu Cys Glu His Phe Cys Val Pro Asn Pro Asp Gln Pro Gly
 290 295 300
 Ser Tyr Ser Cys Met Cys Glu Thr Gly Tyr Arg Leu Ala Ala Asp Gln
 305 310 315 320
 His Arg Cys Glu Asp Val Asp Asp Cys Ile Leu Glu Pro Ser Pro Cys
 325 330 335
 Pro Gln Arg Cys Val Asn Thr Gln Gly Gly Phe Glu Cys His Cys Tyr
 340 345 350
 Pro Asn Tyr Asp Leu Val Asp Gly Glu Cys Val Glu Pro Val Asp Pro
 355 360 365
 Cys Phe Arg Ala Asn Cys Glu Tyr Gln Cys Gln Pro Leu Asn Gln Thr
 370 375 380
 Ser Tyr Leu Cys Val Cys Ala Glu Gly Phe Ala Pro Ile Pro His Glu
 385 390 395 400

Pro	His	Arg	Cys	Gln	Met	Phe	Cys	Asn	Gln	Thr	Ala	Cys	Pro	Ala	Asp
				405				410				415			
Cys	Asp	Pro	Asn	Thr	Gln	Ala	Ser	Cys	Glu	Cys	Pro	Glu	Gly	Tyr	Ile
				420				425				430			
Leu	Asp	Asp	Gly	Phe	Ile	Cys	Thr	Asp	Ile	Asp	Glu	Cys	Glu	Asn	Gly
				435				440				445			
Gly	Phe	Cys	Ser	Gly	Val	Cys	His	Asn	Leu	Pro	Gly	Thr	Phe	Glu	Cys
				450				455				460			
Ile	Cys	Gly	Pro	Asp	Ser	Ala	Leu	Val	Arg	His	Ile	Gly	Thr	Asp	Cys
465				470				475				480			
Asp	Ser	Gly	Lys	Val	Asp	Gly	Gly	Asp	Ser	Gly	Ser	Gly	Glu	Pro	Pro
				485				490				495			
Pro	Ser	Pro	Thr	Pro	Gly	Ser	Thr	Leu	Thr	Pro	Pro	Ala	Val	Gly	Leu
				500				505				510			
Val	His	Ser	Gly												
515															

```
<210> 2
<211> 516
<212> PRT
<213> Homo sapiens
```

<220>
<223> Partial amino acid sequences of a human
thrombomodulin

<400> 2															
Met	Leu	Gly	Val	Leu	Val	Leu	Gly	Ala	Leu	Ala	Leu	Ala	Gly	Leu	Gly
1				5					10					15	
Phe	Pro	Ala	Pro	Ala	Glu	Pro	Gln	Pro	Gly	Gly	Ser	Gln	Cys	Val	Glu
			20					25					30		
His	Asp	Cys	Phe	Ala	Leu	Tyr	Pro	Gly	Pro	Ala	Thr	Phe	Leu	Asn	Ala
		35					40					45			
Ser	Gln	Ile	Cys	Asp	Gly	Leu	Arg	Gly	His	Leu	Met	Thr	Val	Arg	Ser
	50					55					60				
Ser	Val	Ala	Ala	Asp	Val	Ile	Ser	Leu	Leu	Leu	Asn	Gly	Asp	Gly	Gly
65					70					75					80
Val	Gly	Arg	Arg	Arg	Leu	Trp	Ile	Gly	Leu	Gln	Leu	Pro	Pro	Gly	Cys
				85					90					95	
Gly	Asp	Pro	Lys	Arg	Leu	Gly	Pro	Leu	Arg	Gly	Phe	Gln	Trp	Val	Thr
			100					105					110		
Gly	Asp	Asn	Asn	Thr	Ser	Tyr	Ser	Arg	Trp	Ala	Arg	Leu	Asp	Leu	Asn
		115					120					125			

Gly Ala Pro Leu Cys Gly Pro Leu Cys Val Ala Val Ser Ala Ala Glu
 130 135 140
 Ala Thr Val Pro Ser Glu Pro Ile Trp Glu Glu Gln Gln Cys Glu Val
 145 150 155 160
 Lys Ala Asp Gly Phe Leu Cys Glu Phe His Phe Pro Ala Thr Cys Arg
 165 170 175
 Pro Leu Ala Val Glu Pro Gly Ala Ala Ala Ala Val Ser Ile Thr
 180 185 190
 Tyr Gly Thr Pro Phe Ala Ala Arg Gly Ala Asp Phe Gln Ala Leu Pro
 195 200 205
 Val Gly Ser Ser Ala Ala Val Ala Pro Leu Gly Leu Gln Leu Met Cys
 210 215 220
 Thr Ala Pro Pro Gly Ala Val Gln Gly His Trp Ala Arg Glu Ala Pro
 225 230 235 240
 Gly Ala Trp Asp Cys Ser Val Glu Asn Gly Gly Cys Glu His Ala Cys
 245 250 255
 Asn Ala Ile Pro Gly Ala Pro Arg Cys Gln Cys Pro Ala Gly Ala Ala
 260 265 270
 Leu Gln Ala Asp Gly Arg Ser Cys Thr Ala Ser Ala Thr Gln Ser Cys
 275 280 285
 Asn Asp Leu Cys Glu His Phe Cys Val Pro Asn Pro Asp Gln Pro Gly
 290 295 300
 Ser Tyr Ser Cys Met Cys Glu Thr Gly Tyr Arg Leu Ala Ala Asp Gln
 305 310 315 320
 His Arg Cys Glu Asp Val Asp Asp Cys Ile Leu Glu Pro Ser Pro Cys
 325 330 335
 Pro Gln Arg Cys Val Asn Thr Gln Gly Gly Phe Glu Cys His Cys Tyr
 340 345 350
 Pro Asn Tyr Asp Leu Val Asp Gly Glu Cys Val Glu Pro Val Asp Pro
 355 360 365
 Cys Phe Arg Ala Asn Cys Glu Tyr Gln Cys Gln Pro Leu Asn Gln Thr
 370 375 380
 Ser Tyr Leu Cys Val Cys Ala Glu Gly Phe Ala Pro Ile Pro His Glu
 385 390 395 400
 Pro His Arg Cys Gln Met Phe Cys Asn Gln Thr Ala Cys Pro Ala Asp
 405 410 415
 Cys Asp Pro Asn Thr Gln Ala Ser Cys Glu Cys Pro Glu Gly Tyr Ile
 420 425 430

Leu Asp Asp Gly Phe Ile Cys Thr Asp Ile Asp Glu Cys Glu Asn Gly
 435 440 445

Gly Phe Cys Ser Gly Val Cys His Asn Leu Pro Gly Thr Phe Glu Cys
 450 455 460

Ile Cys Gly Pro Asp Ser Ala Leu Ala Arg His Ile Gly Thr Asp Cys
 465 470 475 480

Asp Ser Gly Lys Val Asp Gly Gly Asp Ser Gly Ser Gly Glu Pro Pro
 485 490 495

Pro Ser Pro Thr Pro Gly Ser Thr Leu Thr Pro Pro Ala Val Gly Leu
 500 505 510

Val His Ser Gly
 515

<210> 3

<211> 1548

<212> DNA

<213> Homo sapiens

<220>

<223> Partial base sequences of a human thrombomodulin
 gene

<400> 3

```

atgcttgggg tcctggctct tggcgcgctg gccctggccg gcctgggggt ccccgacccc 60
gcagagccgc agccgggtgg cagccagtgc gtcgagcacg actgcttcgc gctctaccgc 120
ggccccgcga ccttcctcaa tgccagtcag atctgcgacg gactgcgggg ccacctaatg 180
acagtgcgct cctcggtggc tgccgatgtc atttccttgc tactgaacgg cgacggcggc 240
gttgcccgcc ggcgcctctg gatcggcctg cagctgccac ccggtgcgg cgaccccaag 300
cgctcgggc cctgcgcgg cttccagtgg gttacgggag acaacaacac cagctatagc 360
aggtgggcac ggctcgacct caatggggct cccctctgcg gccggttggt cgtcgtctgc 420
tccgctgctg aggcactgt gccagcgag ccgatctggg aggagcagca gtgcgaagtg 480
aaggccgatg gcttcctctg cgagttccac ttcccagcca cctgcaggcc actggctgtg 540
gagcccgggc ccgcgggtgc cgcgctctcg atcacctacg gcaccccggt cgcgggccgc 600
ggagcggact tccaggecgt gccggtgggc agctccgccg cgggtggctcc cctcggttta 660
cagctaattg gcaccgcgcc gcccgaggcg gtccaggggc actgggccag ggaggcgccg 720
ggcgcttggg actgcagcgt ggagaacggc ggctgcgagc acgcgtgcaa tgcgatccct 780
ggggctcccc gctgccagt cccagccggc gccgccctgc aggcagacgg gcgctcctgc 840
accgcatccg cgacgcagtc ctgcaacgac ctctgcgagc acttctgcgt tcccaacccc 900
gaccagccgg gctcctactc gtgcatgtgc gagaccggct accggctggc ggccgaccaa 960
caccggtgcg aggacgtgga tgactgcata ctggagccca gtccgtgtcc gcagcgtgtg 1020
gtcaacacac aggggtggct cgagtgccac tgctacccta actacgaact ggtggacggc 1080
gagtgtgtgg agcccggtga cccgtgcttc agagccaact gcgagtaacca gtgccagccc 1140
ctgaaccaa ctagctacct ctgcgtctgc gccgagggtc tcgcgcccac tccccacgag 1200
ccgcacaggt gccagatggt ttgcaaccag actgcctgtc cagccgactg cgaccccaac 1260
acccaggcta gctgtgagtg ccctgaaggc tacatcctgg acgacggttt catctgcacg 1320
gacatcgacg agtgcgaaaa cggcggtctc tgctccgggg tgtgccaaa cctccccggg 1380
accttcgagt gcatctgcgg gcccgactcg gccctgtgct gccacattgg caccgactgt 1440
gactccggca aggtggacgg tggcgacagc ggctctggcg agcccccgcc cagcccgacg 1500
cccggctcca ccttgactcc tccggccgtg gggctcgtgc attcgggc 1548

```

<210> 4
 <211> 1548
 <212> DNA
 <213> Homo sapiens

<220>

<223> Partial base sequences of a human thrombomodulin gene

<400> 4

```

atgcttgggg tcctggtcct tggcgcgctg gccctggcgg gcctgggggtt cccgcacccc 60
gcagagccgc agccgggtgg cagccagtgc gtcgagcacg actgcttcgc gctctacccg 120
ggccccgcga ccttcctcaa tgccagtacg atctgcgacg gactgcgggg ccacctaata 180
acagtgcgct cctcgggtggc tgccgatgtc atttccttgc tactgaacgg cgacggcggc 240
gttgggccgc ggcgctctg gatcggcctg cagctgccac ccggctgcgg cgaccccaag 300
cgctcggggc cctcgcggcg cttccagtgg gttacgggag acaacaacac cagctatagc 360
aggtggggcac ggctcgacct caatggggct cccctctgcg gccgcttggt cgtcgtctgc 420
tccgctgctg aggccactgt gccagcgag ccgatctggg aggagcagca gtgcgaagtg 480
aaggccgatg gcttcctctg cgagttccac tcccagcca cctgcaggcc actggctgtg 540
gagcccgggc cgcgggtgct gcgcgtctcg atcacctacg gcaccccggt cgcggcccg 600
ggagcggact tccaggcgct gccgggtggc agctccggcg cgggtggctcc cctcggctta 660
cagctaattg gcaccgcgcc gcccgagcgg gtccaggggc actgggcccag ggaggcgccg 720
ggcgcttggt actgcagcgt ggagaacggc ggctgcgagc acgcgtgcaa tgcgatccct 780
ggggctcccc gctgccagtg cccagccggc gccgccttgc aggcagacgg gcgctcctgc 840
accgcatccg cgacgcagtc ctgcaacgac ctctgcgagc acttctgctg tcccaacccc 900
gaccagccgg gctcctactc gtgcatgtgc gagaccggct accggctggc ggccgaccaa 960
caccgggtgc aggacgtgga tgactgcata ctggagccca gtccgtgtcc gcagcgctgt 1020
gtcaacacac aggttggtct cgagtgccac tgctacccta actacgacct ggtggacggc 1080
gagtgtgtgg agcccggtga cccgtgcttc agagccaact gcgagtacca gtgccagccc 1140
ctgaacaaaa ctagtacct ctgctctgct gccgagggct tcgcgcccac tccccacgag 1200
ccgcacaggt gccagatgtt ttgcaaccag actgctgtgc cagccgactg cgaccccaac 1260
accaggtcta gctgtgagtg cctgaaggc tacatcctgg acgacgggtt catctgcacg 1320
gacatcgacg agtgcgaaaa cggcggtctc tgctccgggg tgtgccacaa cctccccggg 1380
accttcgagt gcatctgcgg gcccgactcg gcccttgccc gccacattgg caccgactgt 1440
gactccggca aggtggacgg tggcgacagc ggctctggcg agcccccgcc cagcccgacg 1500
cccggtccca ccttgactcc tccggccgtg gggctcgtgc attcgggg 1548

```

<210> 5
 <211> 21
 <212> DNA
 <213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<220>

<223> Synthetic DNA for mutation

<400> 5

aatgtggcgg gcaagggccg a

21

<210> 6
 <211> 4
 <212> PRT
 <213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
substrate

<400> 6

Leu Ser Thr Arg

1